May Be Linked to Many Diseases

Mysterious, Self-Cloning Microorganism Found

By GEORGE ALEXANDER, *Times Science Writer*

Researchers at UC San Francisco have found a previously unknown kind of infectious microorganism, neither virus nor bacterium, that apparently can make copies of itself in human and animal cells despite the fact that it has no genes to call its own.

Although tests have yet to confirm which specific diseases might be caused by this pathogen, the list of possible illnesses include multiple sclerosis, amyotrophic lateral sclerosis (Lou Gehrig's Disease), Parkinson's disease, diabetes mellitus, rheumatoid arthritis, lupus erythematosis and some cancers.

The pathogen is a small protein for which its discoverer, Dr. Stanley B. Prusiner, has coined the word "prion." It is pronounced "pree-on" and is a combined form of "protein" and "infectious." At this point, Prusiner said, scientists are still speculating as to how the prion copies itself.

Prusiner, a professor of neurology and biochemistry, and a team of colleagues at UC San Francisco and the Veterans Administration Hospital in San Francisco found the pathogen while carrying out research on scrapie, a fatal disease that attacks the central nervous system of sheep.

Their research, which began seven years ago, was aimed at a better understanding of so-called "slow" viruses—viral infections that take anywhere from a few years to several decades to develop.

Scrapie (pronounced "scrapee") has long been thought to be one of many such slow viral diseases. It could be that prions are the

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real cause of these illnesses.

Prusiner and his team took samples of brain tissue from laboratory animals—mice and hamsters—that had been infected with scrapie and had subsequently died. The researchers then began a painstaking, laborious and costly process of purifying the brain tissue, eliminating proteins and other cellular matter that did *not* cause scrapie in other hamsters. They then repeated the process only with that residue that did cause infection.

Expected a Virus

Eventually, they wound up with a small substance that clearly was the infectious agent. They expected to find a virus.

A virus is a parasite. It consists of a small amount of genetic material wrapped inside a protein coat. Once a virus manages to slip inside a host's cell, it then uses the host's genetic machinery to make many copies of its own small set of genes. What happens is that the cell makes so many viral copies that it bursts and releases those viruses to infect still other cells.

But when Prusiner and his coworkers hit the scrapie infectious agent with enzymes that destroy nucleic acids, the building blocks of genes, nothing happened.

"Nucleases didn't change it a bit," Prusiner said of this group of enzymes. "But when we hit it with proteinases (enzymes that destroy proteins), it fell apart."

Reproduce Through Genes

Clearly, then, the infectious agent was either made entirely of protein or, if it contained any genes at all, had only a very small amount well protected inside a protein shell. Through a series of continuing analyses, Prusiner said that they have pretty much eliminated the second possibility.

But all known living creatures, from the smallest to the largest, reproduce themselves through genes —the biological blueprints for future generations. When Prusiner told a meeting of biologists last week in Ventura about a microorganism that apparently replicated without genetic material, he said that "it blew their minds."

How, then, do prions replicate?

"We just don't know yet," Prusiner said in a telephone interview from his UC San Francisco laboratory. "We're looking into several possibilities.

"It could be that all humans and animals already have a gene (in their genetic make up) that codes for diseases like scrapie and this protein merely triggers the gene to begin working. Or it could be that this protein has somehow found a way to reverse biology as we know it and translates for a gene to make more copies of itself. Or maybe it can make copies of itself directly, without genes. That sounds crazy, I realize, but we just don't know right now."

The prion is very small—smaller than even the smallest known virus and smaller than the biological molecule albumin. Prusiner said that it cannot consist of any more than a string of 300 or 500 amino acids, the units of which proteins are made. Albumin is made up of about 700 amino acids.

Prusiner said that his research, supported by the National Institute of Health, the R. J. Reynolds Co and the Howard Hughes Medical Institute, will continue.

His greatest need at present, he said, is for chemical probes that can totally purify prion residues and enable the team to identify the structure of these strange pathogens.